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A5E 300 CG

(71) Applicant
Elan Corporation plc (Irish Republic), Monksland Industrial Estate, Athlone, County Westmeath, Republic of Ireland

(72) Inventors
Edward James Geoghegan,
Randall T. Sparks

(74) Agent and/or address for service
J. A. Kemp & Co., 14 South Square, Gray's Inn, London, WC1R 5EU

(56) Documents cited

GB A	2059764	GB	1205769
GB	1569036	GB	1056259
GB	1478947	EP A2	0002574

(58) Field of search
A5B
A5E
A2B
Selected US specifications from IPC sub-class A61K

(54) Controlled release powder and process for its preparation

(57) A controlled release powder comprises microparticles with an average size in the range 0.1 to 125 μm, each of the microparticles being in the form of a micromatrix of an active ingredient uniformly distributed in at least one non-toxic polymer. The microparticles have a predetermined release of active ingredient when the dissolution rate thereof is measured according to the Paddle Method of U.S. Pharmacopoeia XX at 37°C and 75 r.p.m. The active ingredient may be especially a drug and also a herbicide, pesticide, sweetening or flavouring agent. The powder can be encapsulated into gelatin capsules, or formed into ointments, suspensions etc.

GB 2 166 651 A

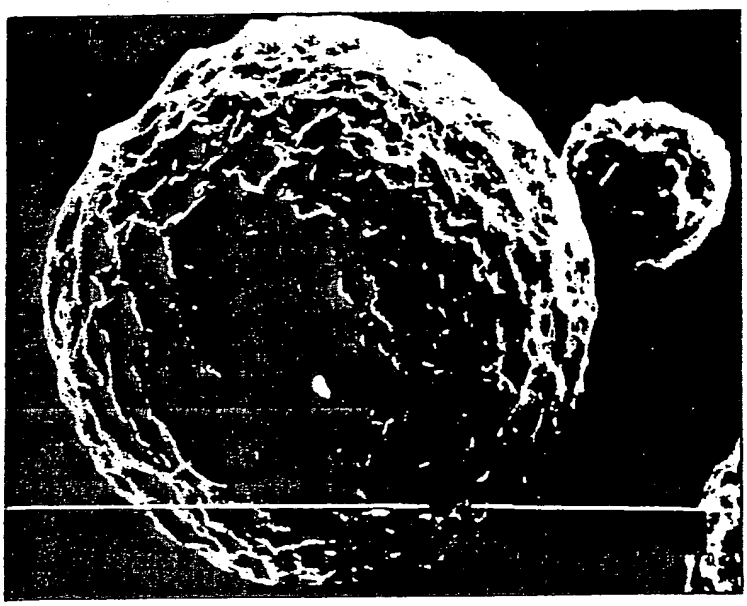

FIG. 1.

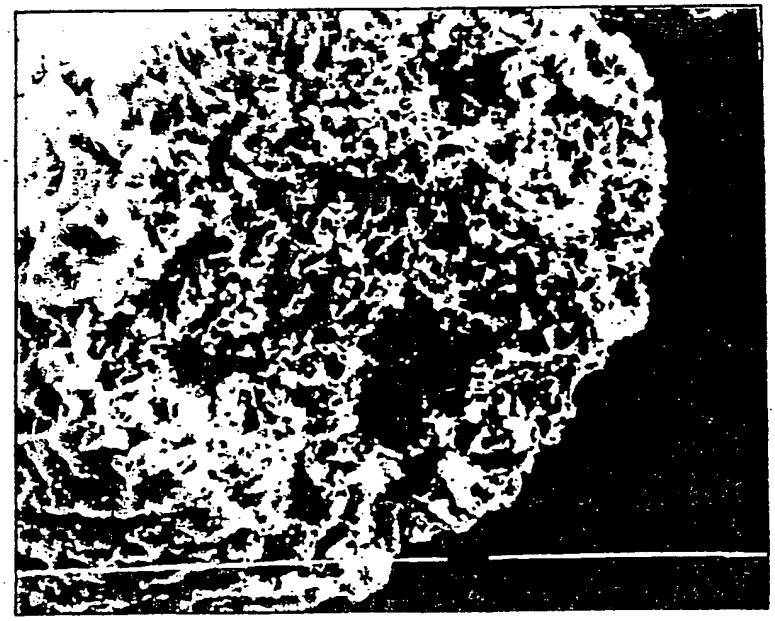

FIG. 2.

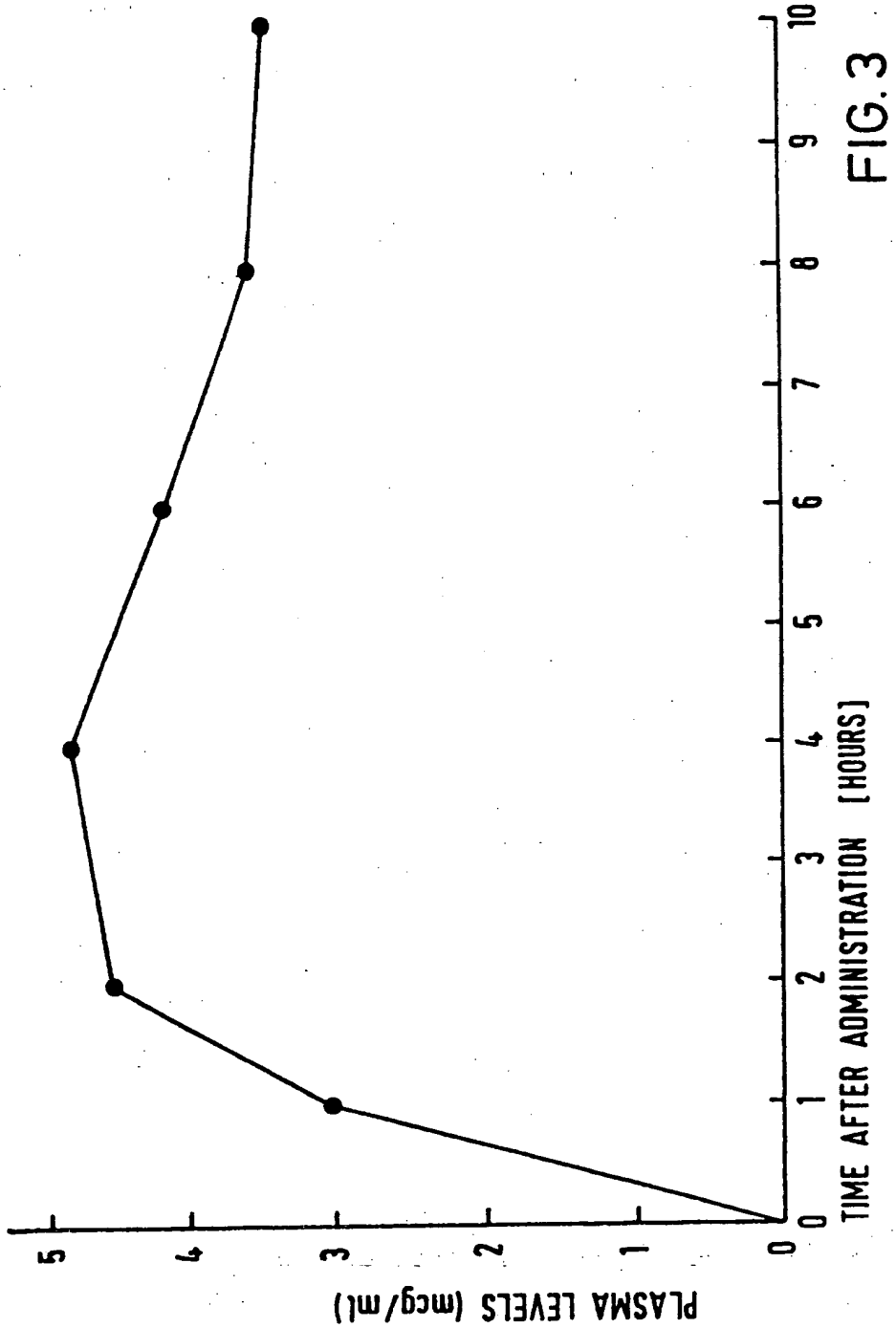
PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
TIME AFTER ADMINISTRATION (HOURS)
0
1
2
3
4
5
6
7
8
9
10

FIG. 3

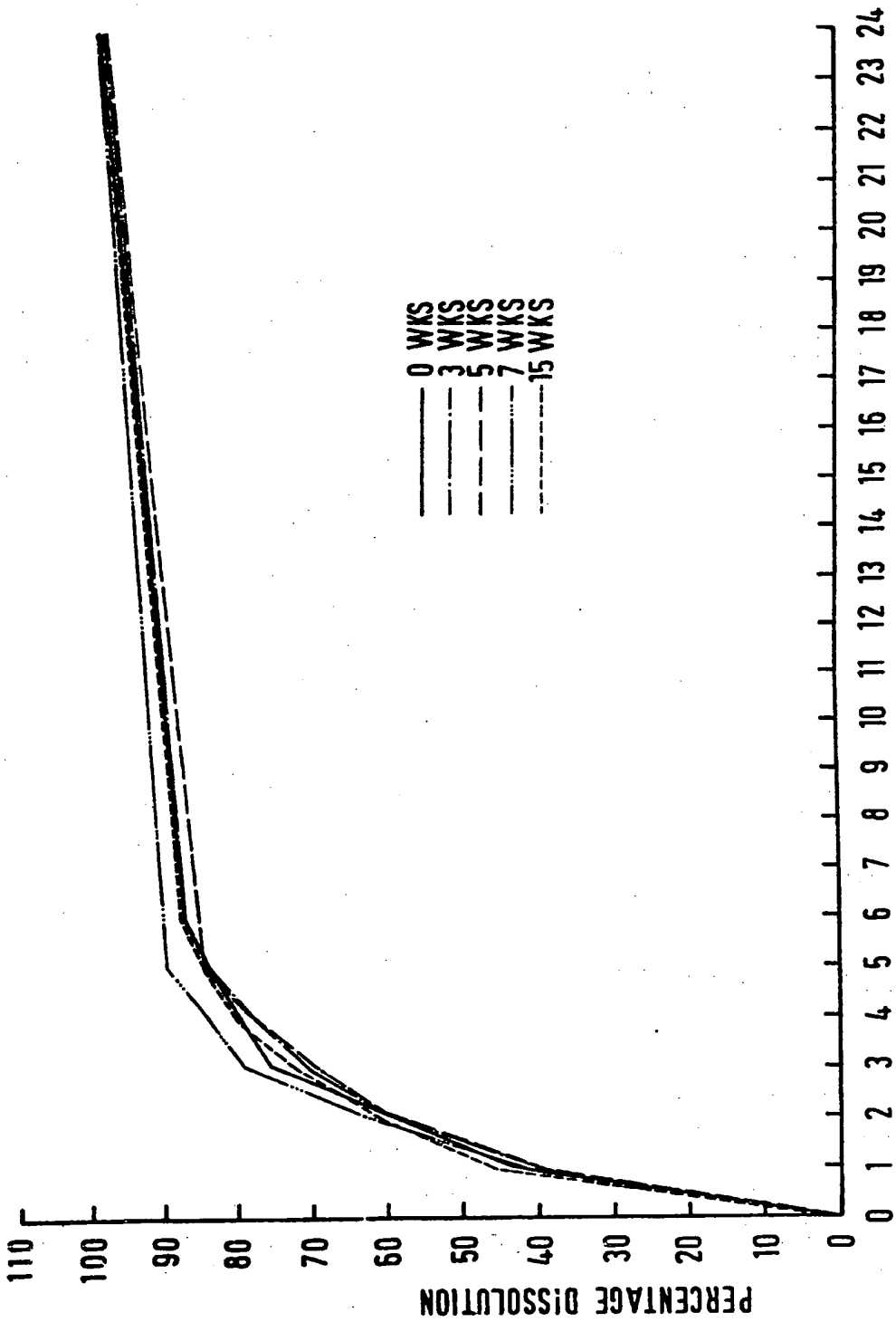
PERCENTAGE DISSOLUTION
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
TIME [HOURS]
0 WKS
3 WKS
5 WKS
7 WKS
15 WKS

FIG.4

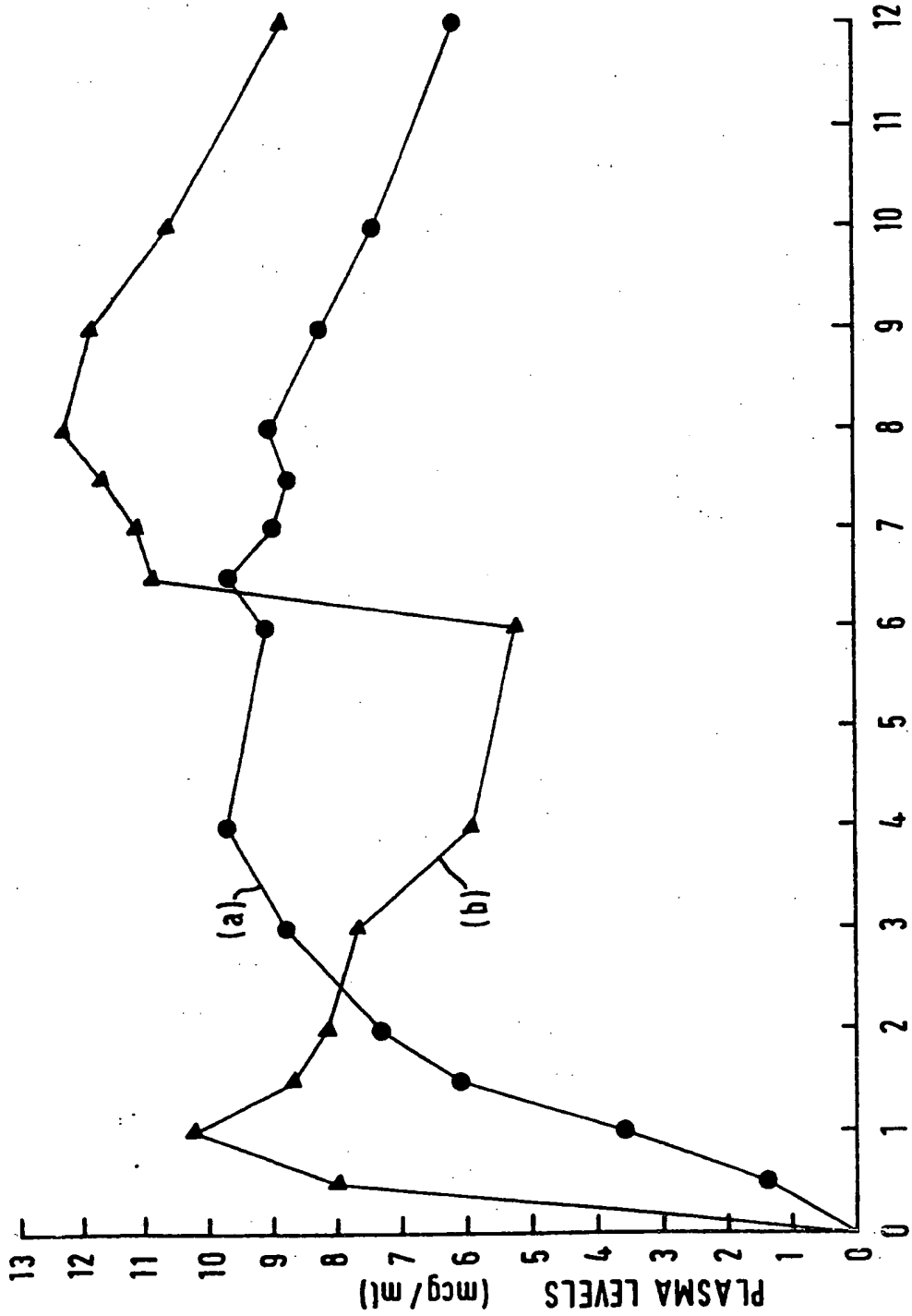
PLASMA LEVELS (mcg/ml)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12
TIME AFTER ADMINISTRATION [HOURS]
(a)
(b)

FIG.5

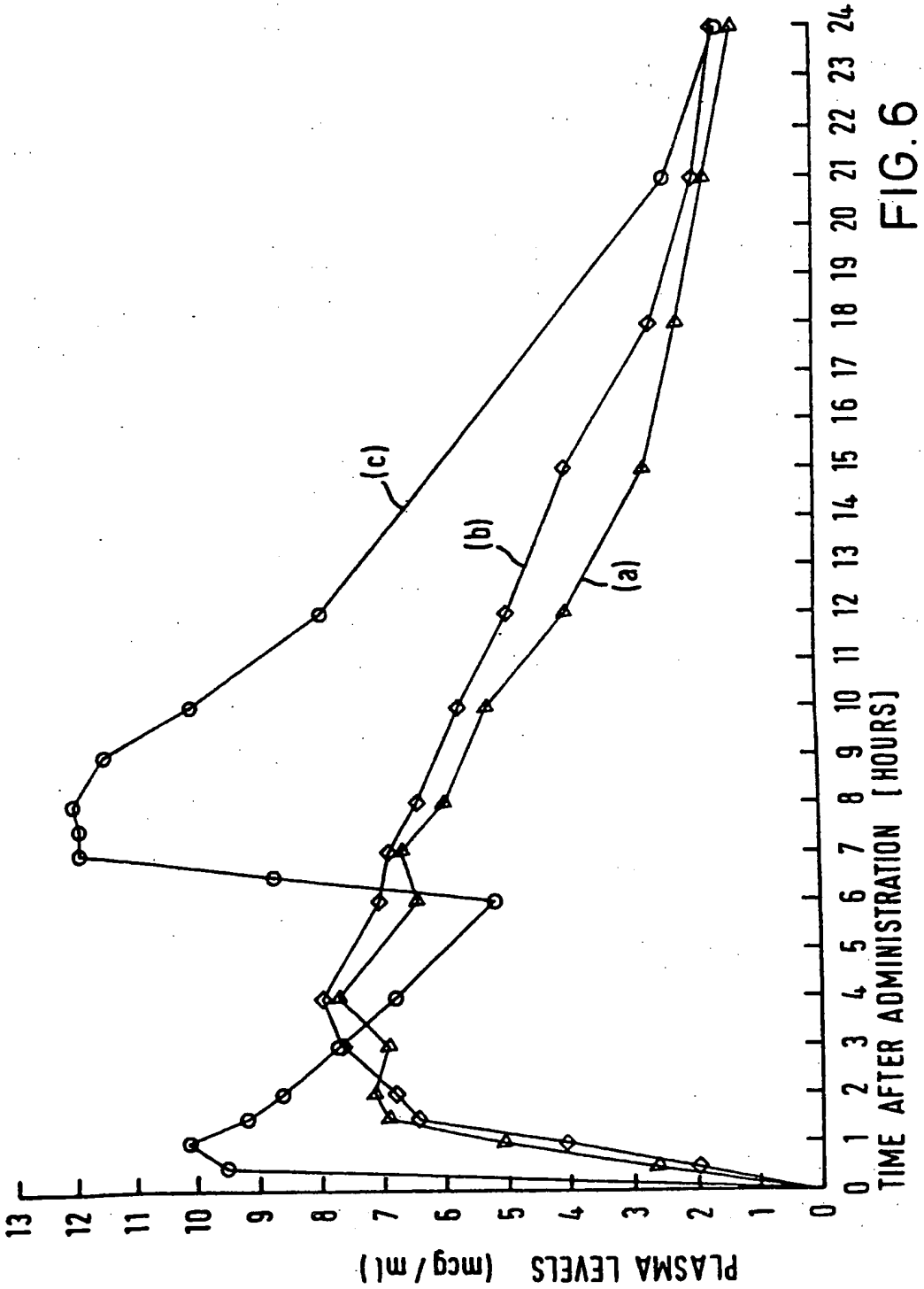
PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
TIME AFTER ADMINISTRATION (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
(a)
(b)
(c)

FIG. 6

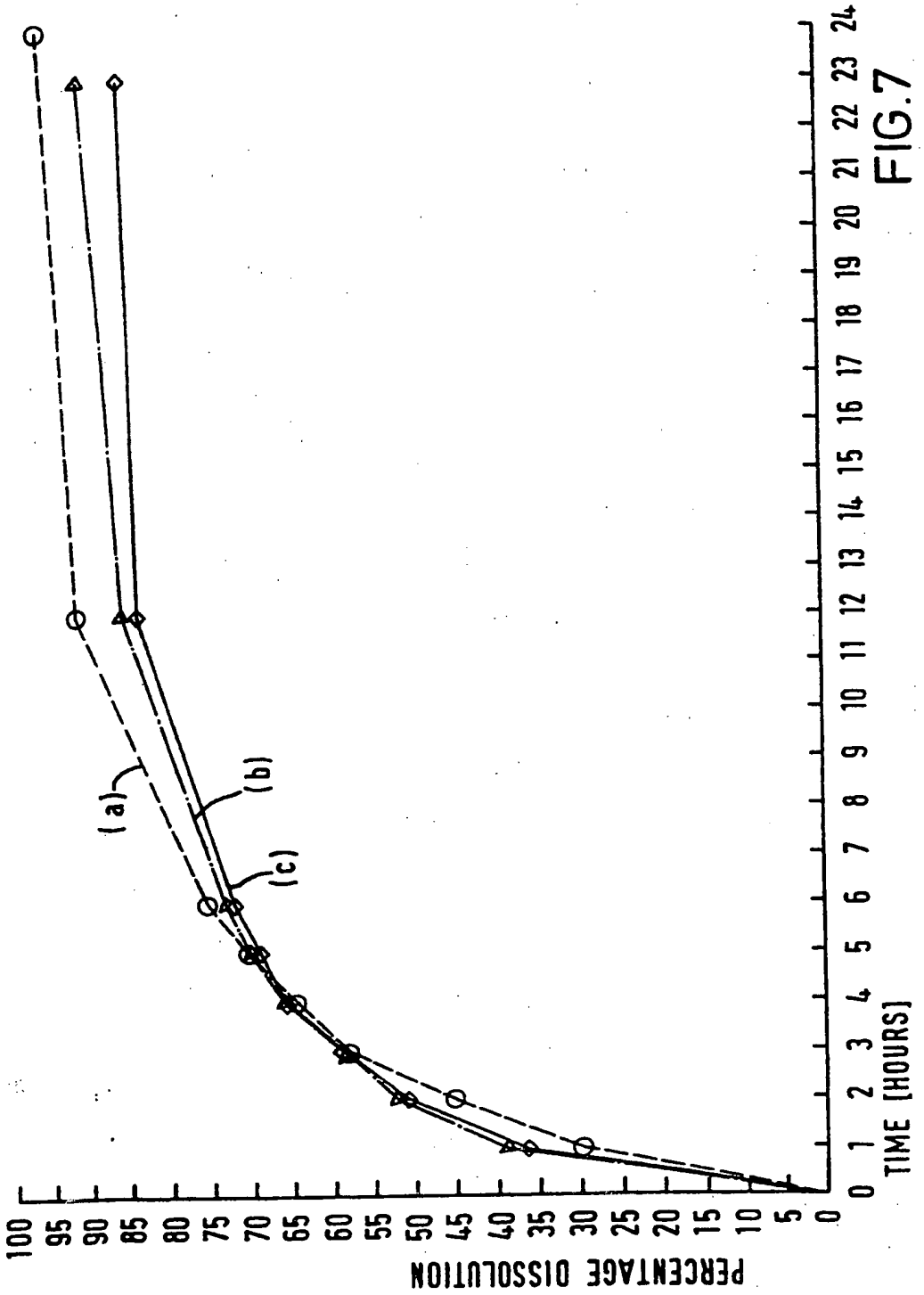
PERCENTAGE DISSOLUTION
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
TIME [HOURS]
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
(a)
(b)
(c)

FIG.7

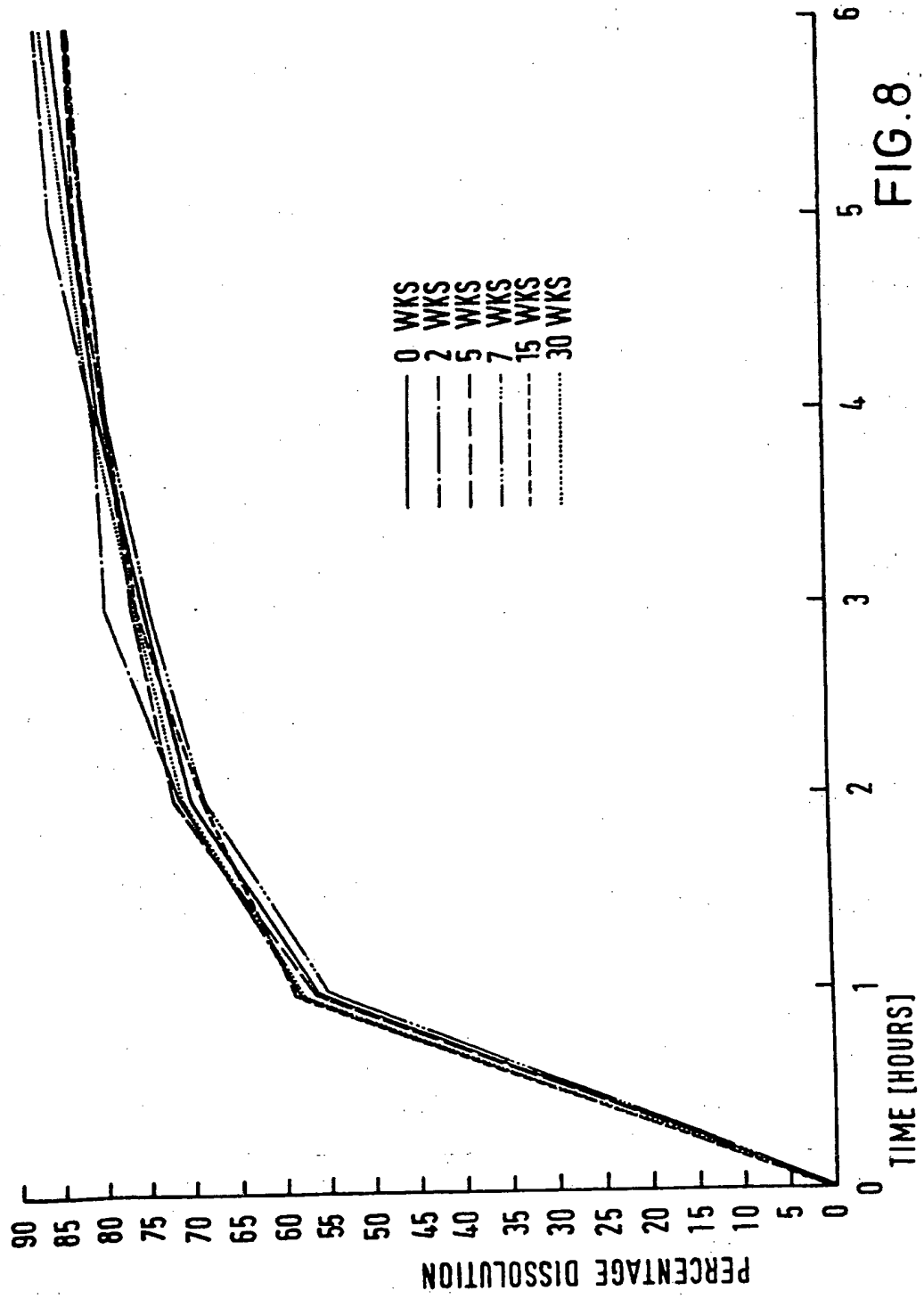
PERCENTAGE DISSOLUTION
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
TIME [HOURS]
0
1
2
3
4
5
6
0 WKS
2 WKS
5 WKS
7 WKS
15 WKS
30 WKS

FIG.8

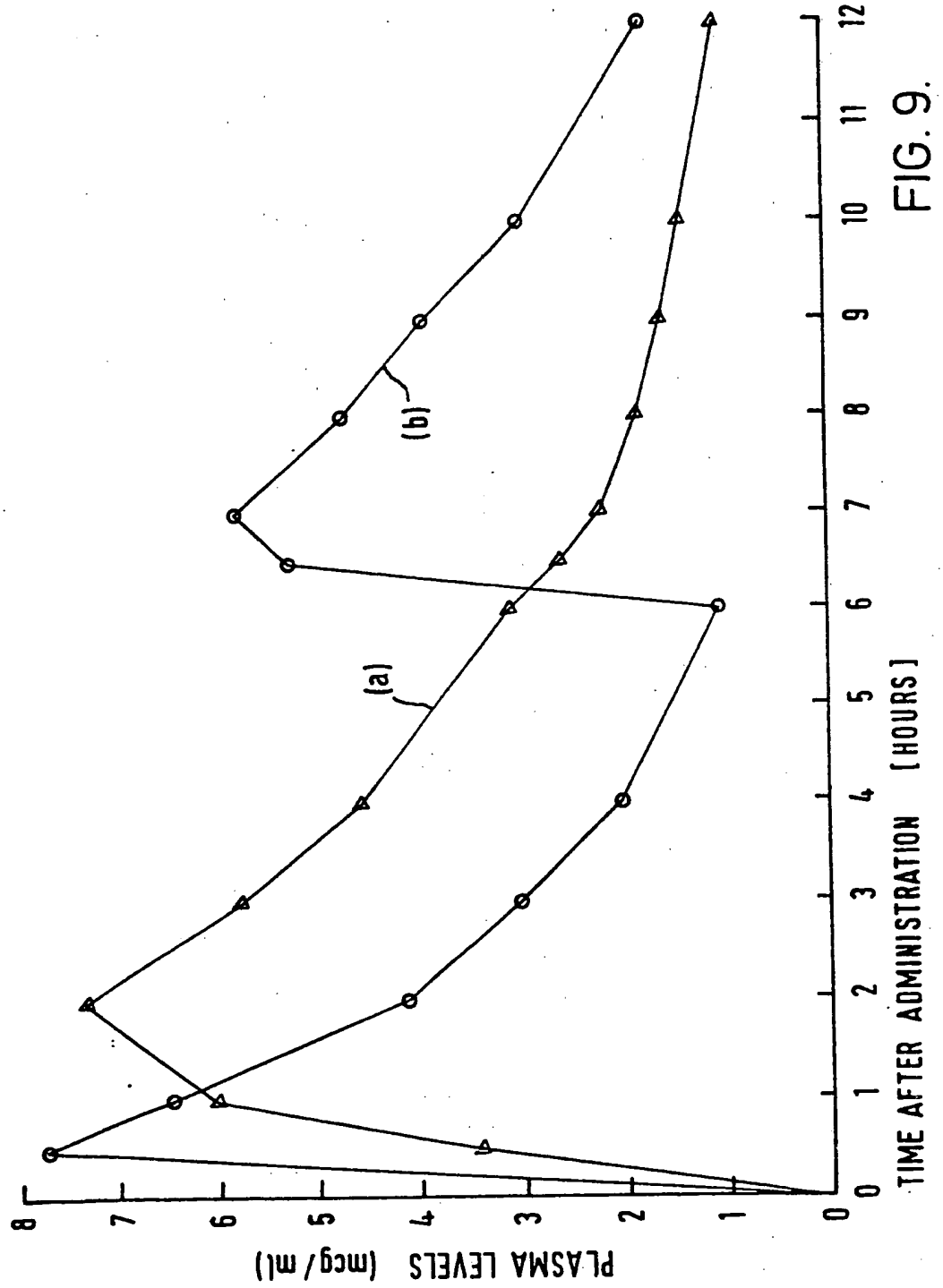
PLASMA LEVELS (mcg/ml)
TIME AFTER ADMINISTRATION (HOURS)
(a)
(b)
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 9.

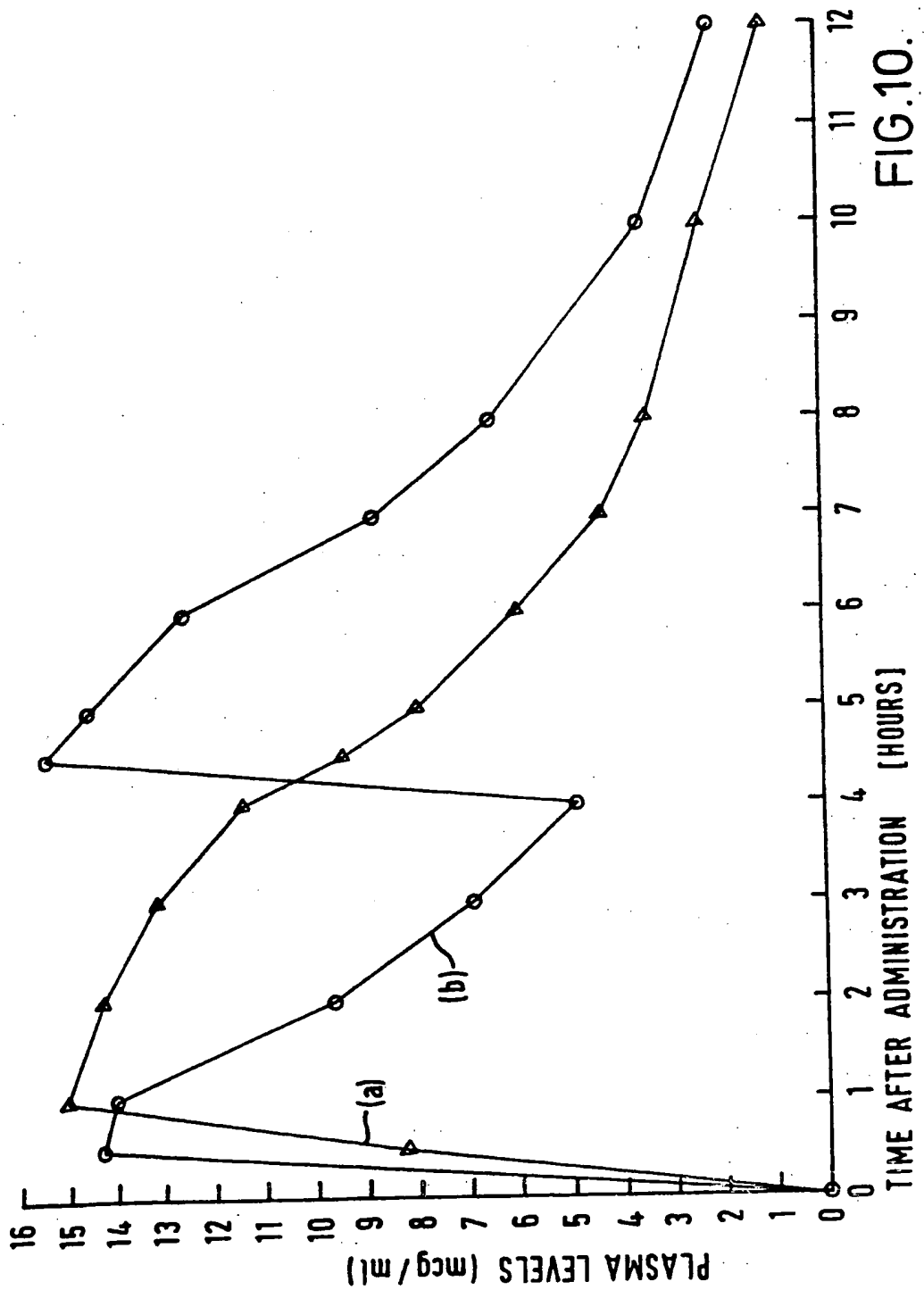

FIG.10.

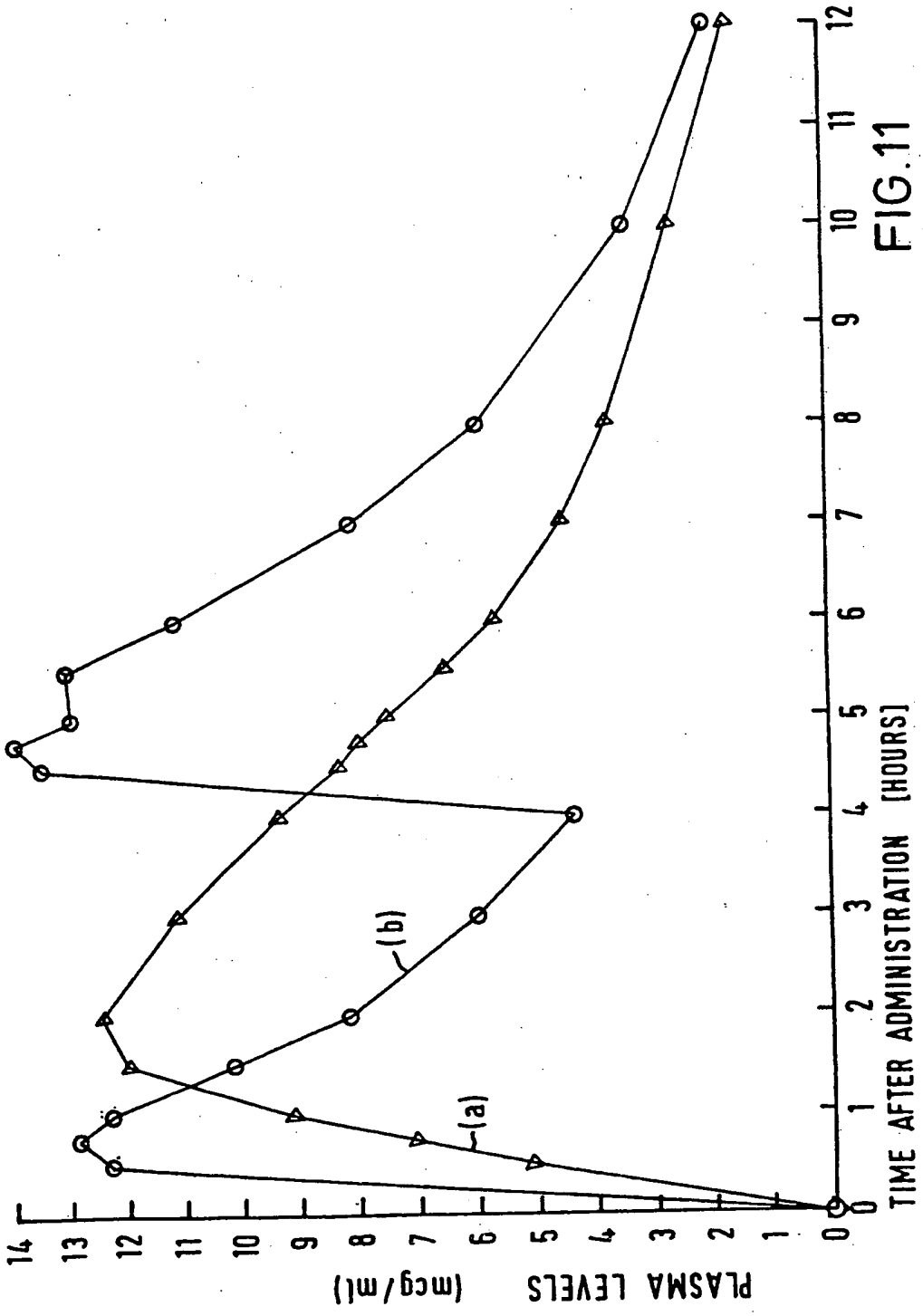
PLASMA LEVELS (mcg/ml)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
TIME AFTER ADMINISTRATION [HOURS]
0
1
2
3
4
5
6
7
8
9
10
11
12
(a)
(b)

FIG.11

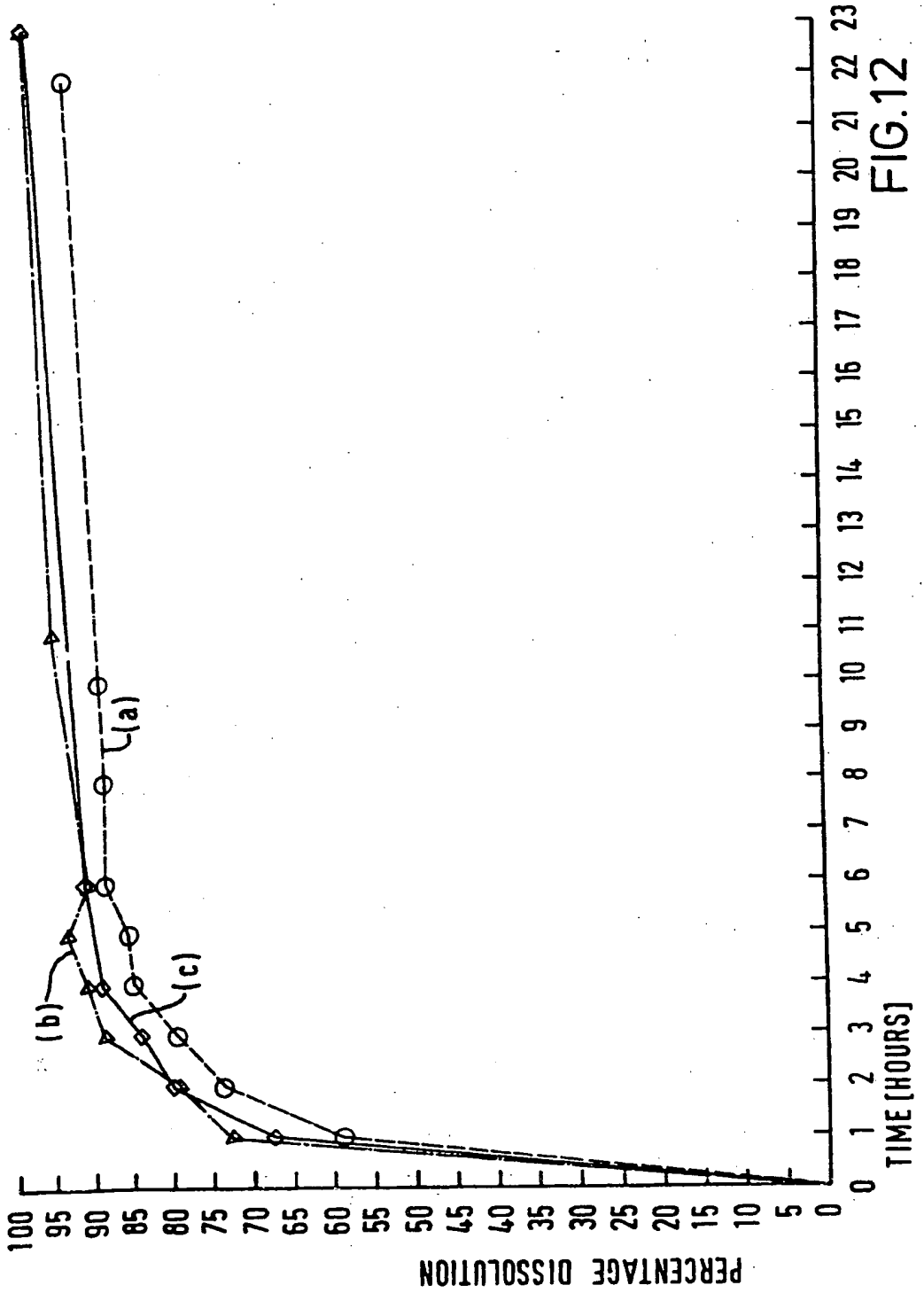
PERCENTAGE DISSOLUTION
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
TIME (HOURS)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
(a)
(b)
(c)

FIG.12

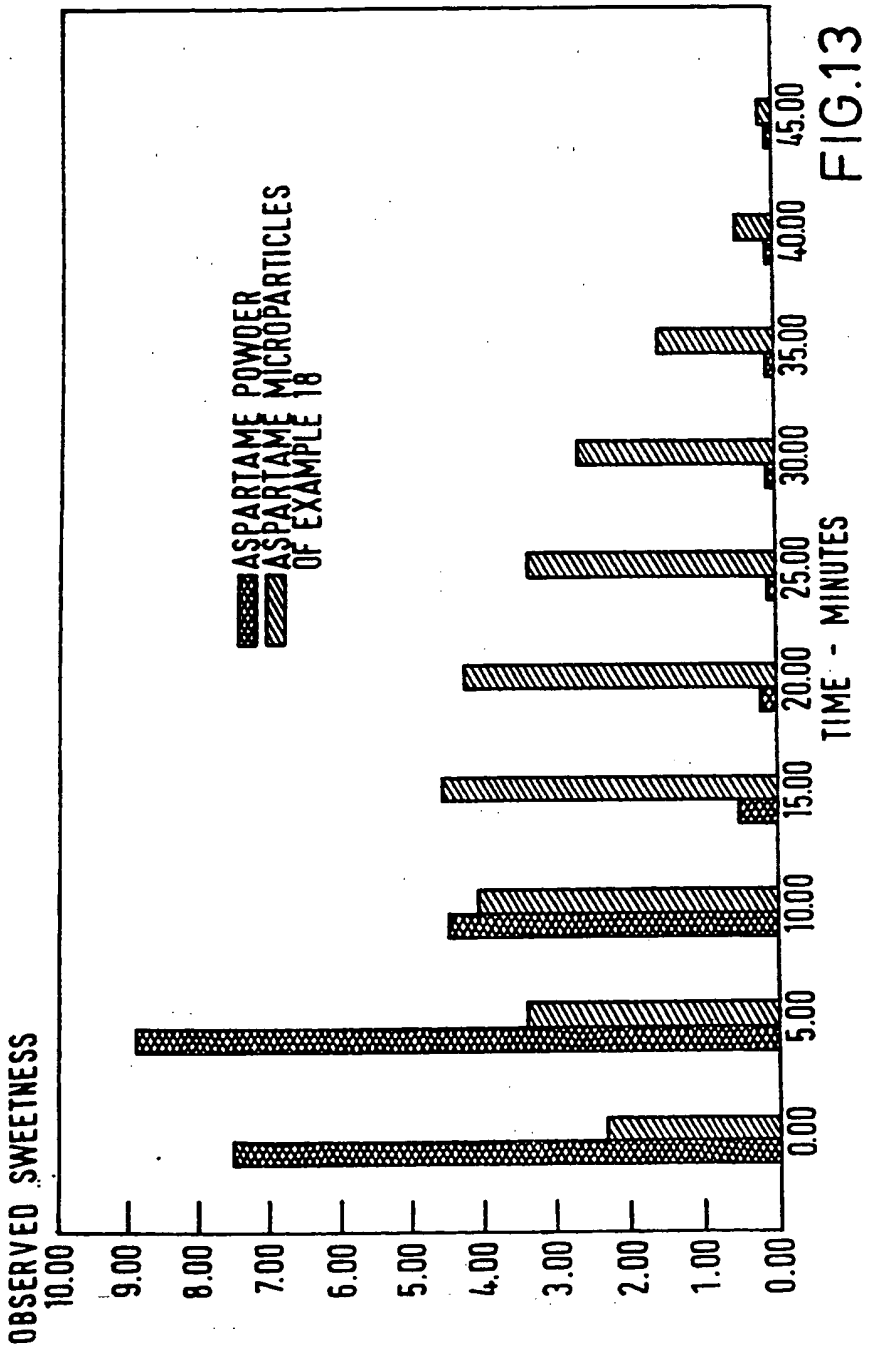
OBSERVED SWEETNESS
10.00
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
ASPARTAME POWDER
ASPARTAME MICROPARTICLES OF EXAMPLE 18
0.00
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
TIME - MINUTES

FIG.13

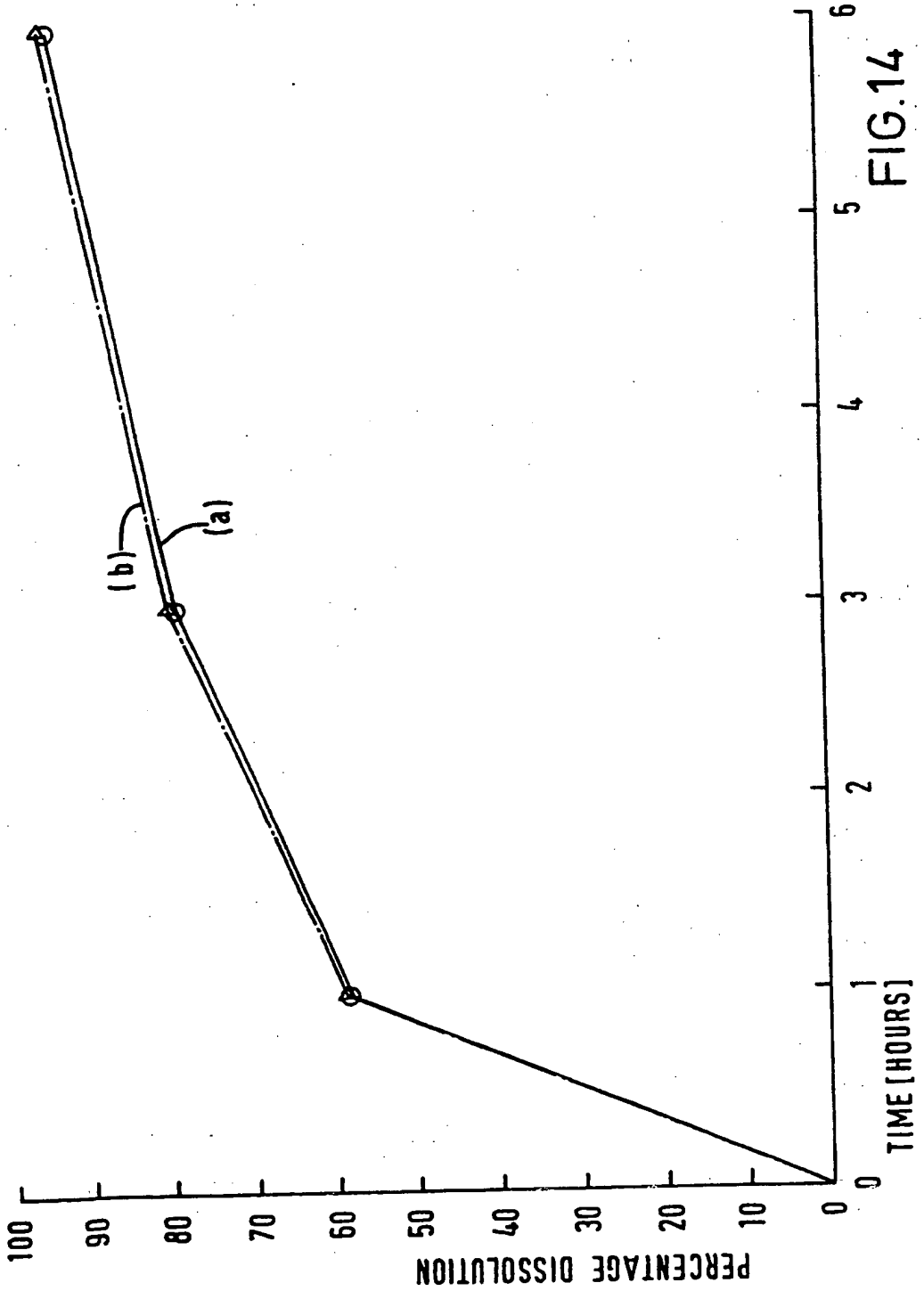
PERCENTAGE DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
TIME [HOURS]
0
1
2
3
4
5
6
(a)
(b)

FIG.14

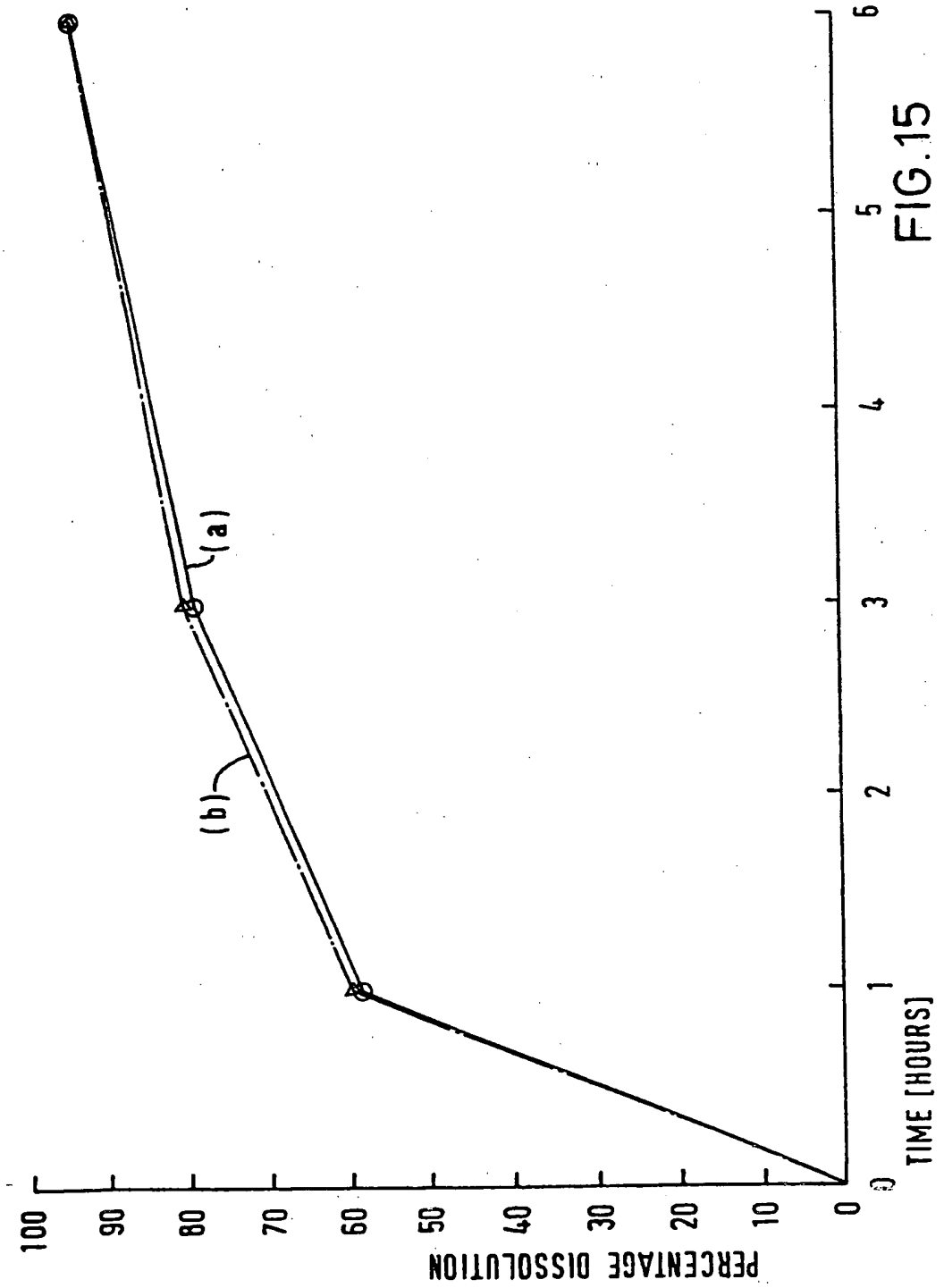
PERCENTAGE DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
TIME [HOURS]
0
1
2
3
4
5
6
(a)
(b)

FIG.15

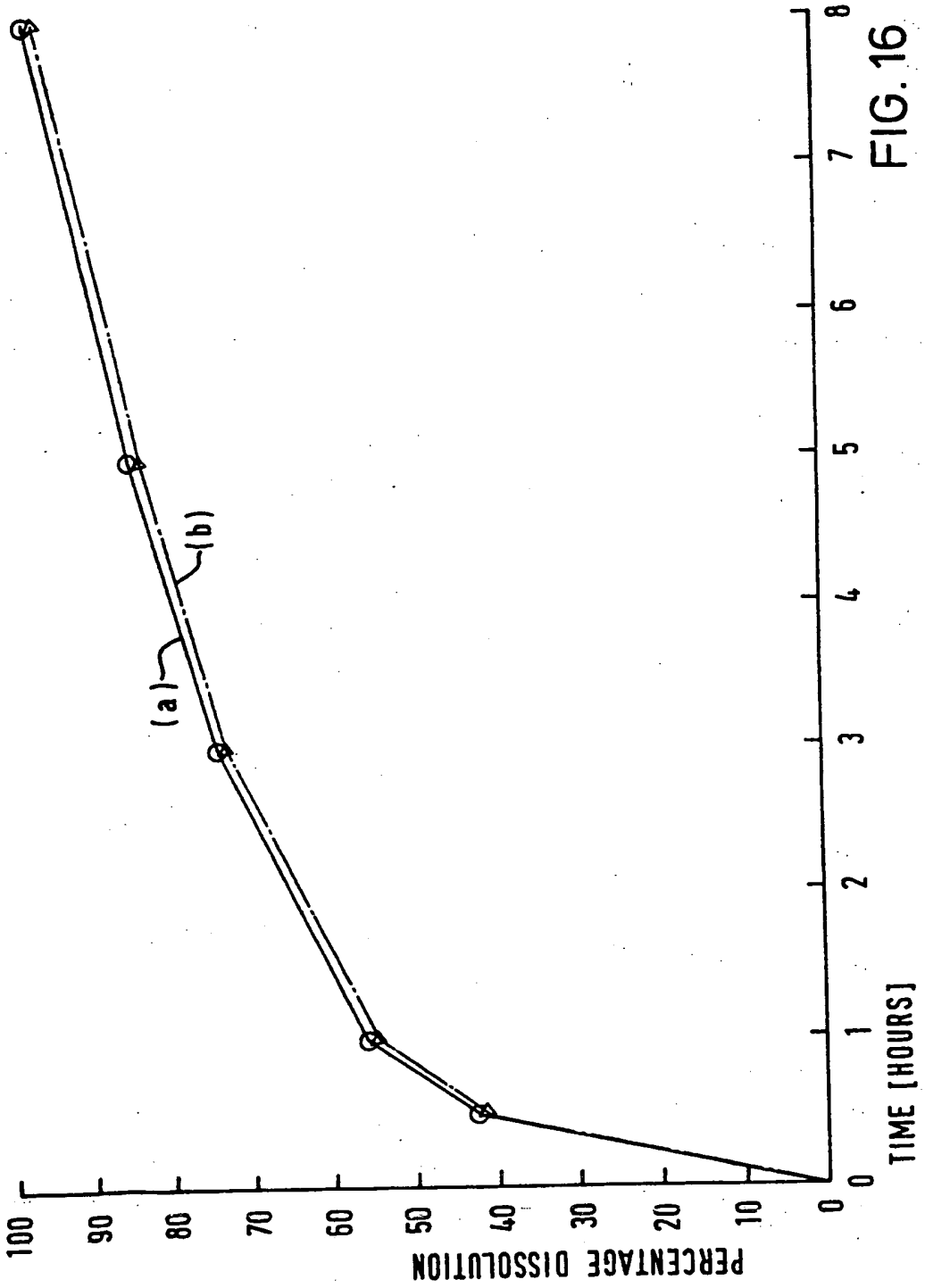
PERCENTAGE DISSOLUTION
100
90
80
70
60
50
40
30
20
10
0
TIME [HOURS]
0
1
2
3
4
5
6
7
8
(a)
(b)

FIG. 16

SPECIFICATION

Controlled Release Powder and Process for its Preparation

This invention relates to controlled release formulations and, in particular, to sustained release powders consisting of discrete micro-particles.

Many types of controlled or sustained release pellets are known which are loaded into capsules for oral administration. These pellets can be described as macro-particles and invariably have an average size greater than 400 µm. Such pellets are the subject, for example, of the Applicants' EP—A—0 122 077, EP—A—0 123 470, EP—A—0 156 077 and EP—A—0 149 920.

Sustained release pellets cannot be readily formulated as liquids. Sustained release liquids are desirable for use as geriatric and paediatric formulations.

Various processes are known for the production of micro-spheres using solvent evaporation emulsion techniques. Known micro-encapsulation techniques are generally employed for phase transformation, such as for the conversion of liquids to solids. Alternatively, such techniques may be used for protecting an active material, such as coating aspirin to mask its stomach irritant properties.

Sustained release liquids are known which contain ion exchange resins. In such sustained release liquids the active ingredient is bound to an ion exchange resin in the form of a reversible complex and is displaced therefrom *in vivo*. Such sustained release liquids are described, for example, in French Patent Publication No. 2 278 325.

It is an object of the present invention to provide a controlled release powder of discrete micro-particles which can be readily formulated in liquid form but which can also be formulated in other sustained release forms such as tablets which have improved properties relative to the known forms.

Accordingly, the invention provides a controlled release powder containing discrete micro-particles for use in edible pharmaceutical and other sustained release compositions, said powder comprising particles containing an active ingredient and optionally an excipient in intimate admixture with at least one non-toxic polymer, each of said particles being in the form of a micromatrix with active ingredient and the excipient, if preseent, uniformly distributed throughout the polymer, said particles having an average size of between 0.1 and 125 µm and having a predetermined release of active ingredient when the dissolution rate thereof is measured according to the Paddle Method of U.S. Pharmacopoeia XX at 37°C and 75 r.p.m.

Preferably, the particles have an average size of between 5 and 100 µm.

The Applicants have coined the term "pharmasomes" for the micro-particles of the powder according to the invention and which term is used hereinafter in the Specification.

The controlled release powders according to the invention can permit a sustained release of active ingredient as hereinafter demonstrated.

Further preferably, the active ingredient is a drug, a nutrient, a colouring agent, a fragrance, a herbicide, a pesticide, a flavouring agent or a sweetening agent.

The powder can be dispersed or suspended in a liquid vehicle and will maintain its sustained release characteristics for a useful period of time. Such dispersions or suspensions have both chemical stability and stability in terms of dissolution rate.

The polymer may be soluble, insoluble, permeable, impermeable or biodegradable. The polymers may be polymers or co-polymers. The polymer may be a natural or synthetic polymer. Natural polymers include polypeptides, polysaccharides and alginic acid. A suitable polypeptide is zein and a suitable polysaccharide is cellulose.

Representative synthetic polymers include alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic acids and esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes and polyurethanes and co-polymers thereof.

Particularly suitable polymers include: methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), poly(ethylene), poly(ethylene) low density, poly(ethylene) high density, poly(propylene), poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohol), poly(vinyl isobutyl ether), poly(vinyl acetate), poly(vinyl chloride) and polyvinylpyrrolidone.

Especially suitable co-polymers include butyl methacrylate isobutyl methacrylate co-polymer, high molecular weight, methylvinyl ether/maleic acid co-polymer, methylvinyl ether/maleic acid, monoethyl ester co-polymer, methylvinyl ether/maleic anhydride co-polymer and vinyl alcohol/vinyl acetate co-polymer.

Representative biodegradable polymers include, polyglycolides, poly(ethylene terephthalate) and polyurethane.

Representative acrylates and methacrylates are polymers sold under the Trade Mark Eudragit.

When the active ingredient is a drug there is essentially no limitation on the type of drug which may be used.

Representative active ingredients include antacids, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, anti-histamines, laxatives, decongestants, vitamins, gastro-intestinal sedatives, anti-diarrheal preparations, anti-anginal drugs, vasodilators, anti-arrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anti-coagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycaemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, bronchodilators, expectorants, cough supressants, mucolytics and anti-uricemic drugs.

Typical active ingredients include gastro-intestinal sedatives such as metoclopramide and propantheline bromide, antacide such as aluminium trisilicate, aluminium hydroxide and cimetidine, anti-inflammatory drugs such as phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone and prednisolone, coronary vasodilator drugs such as glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate, peripheral and cerebral vasodilators such as soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine and nicotinic acid, anti-infective substances such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate and hexamine hippurate, neuroleptic drugs such as flurazepam, diazepam, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylimipramine, central nervous stimulants such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride, antihistamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine, anti-diarrheal drugs such as bisacodyl and magnesium hydroxide, the laxative drug, dioctyl sodium sulfosuccinate, nutritional supplements such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine, anti-spasmodic drugs such as dicyclomine and diphenoxylate, drugs affecting the rhythm of the heart such as verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate, drugs used in the treatment of hypertension such as propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril and hydralazine, drugs used in the treatment of migraine such as ergotamine, drugs affecting coagulability of blood such as epsilon aminocaproic acid and protamine sulfate, analgesic drugs such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid, anti-epileptic drugs such as phenytoin sodium and sodium valproate, neuromuscular drugs such as dantrolene sodium, substances used in the treatment of diabetes such as tolbutamide, disbenase glucagon and insulin, drugs used in the treatment of thyroid gland disfunction such as triiodothyronine, thyroxine and propylthiouracil, diuretic drugs such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and triamterene, the uterine relaxant drug ritodrine, appetite suppressants such as fenfluramine hydrochloride, phentermine and diethylproprion hydrochloride, anti-asthmatic and bronchodilator drugs such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate, expectorant drugs such as guaiphenesin, cough suppressants such as dextromethorphan and noscapine, mucolytic drugs such as carbocisteine, anti-septics such as cetylpyridinium chloride, tyrothricin and chlorhexidine, decongestant drugs such as phenylpropanolamine and pseudoephedrine, hypnotic drugs such as dichloralphenazone and nitrazepam, antinauseant drugs such as promethazine theoclate, haemopoietic drugs such as ferrous sulphate, folic acid and calcium gluconate, uricosuric drugs such as sulphinpyrazone, allopurinol and probenecid.

Particularly preferred active ingredients are: ibuprofen, paracetamol, 5-amino-salicylic acid, dextromethorphan, propranolol, theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diazepam, diclofenac, indomethacin, amoxycillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, co-dergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, lorazepam, glibenclamide, salbutamol, trimethoprim/sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin, potassium chloride and metoprolol tartrate.

Especially preferred active ingredients include theophylline, paracetamol and potassium chloride.

The active ingredient may also be a saccharin for use in edible compositions wherein it is desired to obtain a controlled release of saccharin, such as, for example in chewing gums. The active ingredient may also be other sweetening agents, such as, for example, aspartame which is especially suitable for use in chewing gums.

The invention also provides a process for preparing the controlled release powder according to the invention which comprises:

a) forming a solution of the polymer or polymers in a solvent;

b) dissolving or dispersing the active ingredient in said polymer solution so as to form a uniform mixture; and

c) removing the solvent from the mixture so as to obtain micro-particles having an average size in the range 0.1 to 125 µm.

The solvent is selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof.

Especially preferred solvents include, water, hexane, heptane, methanol, ethanol, acetone, methylethyl ketone, methylisobutyl ketone, methylene chloride, chloroform, carbon tetrachloride, toluene, xylene and tetrahydrofuran.

The choice of solvent or solvents will be dictated by the particular polymer or polymers selected. For example, suitable solvents for use with the celluloses are acetone or a mixture of methanol and methylene chloride.

The concentration of the polymer in the solvent will normally be less than 75% by weight. Normally the concentration will be in the range of 10—30% by weight.

If the active ingredient is not soluble in the polymer solution the particle size of the active ingredient is reduced to less than 10 µm. The reduction of particle size may be achieved by milling, for example, by ball milling or jet milling.

The active ingredient may, of course, be a liquid.

The ratio of drug to polymer will very within wide limits, such as within the range 0.1:10 to 10:1.

The uniform mixture of the active ingredient in the polymer solution may be achieved by rapid and continuous mixing.

The removal of the solvent and the formation of particles of the desired size may be achieved in a number of ways.

1. Spray Drying

The mixture of active ingredient and polymer in the solvent is sprayed into a stream of hot air in conventional manner. This causes the solvent to evaporate and the powder is collected in the spray drying vessel.

The size of the particles may be controlled in a number of ways, for example, by pre-selecting the inlet and outlet temperature of the spray drying vessel; the rate of introduction of the spray, the size of the spray tip or the ratio of the concentration of active ingredient to polymer.

2. Use of an External Liquid Phase

The mixture of active ingredient and polymer, which is in the form of a solution or suspension, is poured into a liquid external phase. The liquid external phase comprises a solvent which is immiscible or partially immiscible with the active ingredient/polymer mixture.

The choice of external liquid phase will be determined by the particular combination of active ingredient and polymer selected. Suitable liquids for the external liquid phase include water, aqueous solutions, for example, sugar solutions, organic solvents, mineral oil, vegetable oils, fixed oils, syrups or silicones. The aqueous solution may include a thickening agent, such as xanthan gum, to increase the viscosity thereof. Oils may be made more viscous by the addition of substances such as magnesium stearate. The external liquid phase may also comprise a solution of a different pH, for example, a buffer.

The ratio of external liquid phase to polymer mixture will be at least 2:1.

Following addition of the active ingredient/polymer mixture to the external liquid phase, the two phase mixture obtained is emulsified, for example, by rapid mixing. The emulsion formed may be either stable or unstable. Globules of the active ingredient/polymer are thereby formed in the emulsion.

The solvent may be removed in a number of ways. If the solvent is volatile it can be removed passively. For example, if the solvent is acetone it would normally be removed by evaporation during the mixing step. The particles formed are then harvested by filtration or centrifugation.

The solvent can also be removed by heating while mixing the two phase mixture. For example, the solvent may be removed on a rotary film evaporator. The solvent may also be removed under vacuum with or without heating. Microwave drying may also be employed with or without the application of a vacuum. Another mode of solvent removal is freeze drying.

After harvesting of the micro-particles, they will normally be given successive washings with a suitable solvent, followed by drying.

For example, when the solvent used is acetone and the external liquid phase is mineral oil, then the micro-particles will be given successive washings with hexane and dried at 45°C.

On a commercial scale emulsification of the mixture may be achieved by emulsification with an in-line mixer or mixers.

The particle size may be controlled in a number of ways. For example, the particle size may be controlled by the rate of mixing, the viscosity of the external liquid phase, the viscosity of the internal phase, the active ingredient particle size of the volatility of the solvent.

3. Other Methods for the Removal of the Solvent Include Phase Separation, Interfacial Polymer Deposition and Coacervation

The optional excipient used in association with the or each active ingredient will frequently have an

active role to play following administration. For example, the excipient may be a surface-active agent which facilitates the transport of water into the particles, for example, sodium lauryl sulphate or a surface-active agent sold under the Trade Mark Tween. The excipient may also be an active transport agent such as, for example, glucose or one or more amino acids.

The excipient may comprise one or more organic acids which facilitate the dissolution of drugs which are poorly soluble in alkaline media. Such acids include, for example, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid and tartaric acid. Similarly, the excipient may comprise one or more basic materials which facilitate the dissolution of drugs which are poorly soluble in acid media. Such basic materials include sodium carbonate, sodium citrate and sodium bicarbonate.

When the active ingredient is a drug, the micro-particles according to the invention may be formulated in a wide variety of forms. Pharmaceutical formulations according to the invention include pills and tablets, for example, coated tablets, effervescent tablets, chewable tablets, moulded tablets and melt tablets. The particles according to the invention may be compressed into tablets and optionally coated without any substantial change occurring in the particles. Furthermore, because of the micro-particulate nature of the particles they are unlikely to be significantly degraded or ground by any chewing action.

Powder formulations according to the invention include dusting powders and douche powders.

The particles according to the invention may also be loaded into capsules which may be either soft gelatin capsules or hard gelatin capsules.

Other solid dosage forms include pessaries, rectal suppositories, vaginal tablets and vaginal inserts.

The particles according to the invention may also be used in implants and ocular inserts.

The powders can also be formulated in forms suitable for topical application, such as, for example, as creams or ointments and for transdermal delivery, for example, in the form of transdermal patches.

The micro-particulate powders according to the invention may also be used in the form of foams, gels, pastes, gums, mucilages and jellies.

Other suitable formulations incorporating the microparticles according to the invention include inhalants, magmas, intrauterine devices, patches, biodegradable wound dressings and other topical dressings.

The micro-particulate powders according to the invention are especially suitable for formulation as liquids for oral, local or parenteral administration. Thus, they can be formulated in liquid form for use as eye drops, nasal drops, ear drops, suspensions, syrups, infusion and injectable solutions. The powders can also be formulated as nasal sprays. The injectable solutions include intravenous, subcutaneous and intramuscular injectable solutions.

The oral suspensions and syrups according to the invention are particularly suitable for use in geriatric and paediatric medicine. The liquids formed have good mouth feel. Furthermore, because the polymer substantially coats the active ingredient, the coating masks any unpleasant taste.

A characteristic of good mouth feel also applies to chewable and effervescent tablets. Because of the micro-particulate nature of the powder one does not experience a granular sensation.

Preferred paediatric liquids according to the invention are suspensions or syrups of bronchial relaxants, analgesice, anti-pyretics, anti-tussives, anti-spasmodics, anti-nauseants, anti-histamines, anti-epileptics and antibiotics.

Other especially suitable liquid formulations according to the invention are non-aqueous suspensions of highly water soluble or water insoluble active ingredients. Suitable drugs for formulating in this way include dextromethorphan, guaiphenesin and pseudoephedrine or a salt thereof or potassium chloride.

The liquid formulations have good shelf life and demonstrate stability both in chemical terms and in terms of dissolution rates up to thirty days. It is estimated that the shelf life can be as long as five years.

In the liquid formulations according to the invention one can achieve a concentration of active ingredient of up to 1 g per 5 ml.

Heretofore many drugs have not been stable in liquid form, for example, analgesics, necessitating a dosage regimen of every 4—6 hours. The liquids according to the invention offer versatility and the possibility of twice daily administration for a medicament such as, for example, analgesics, anti-histamines and bronchial relaxants.

The taste masking feature of the powders according to the invention is of significant importance in the area of paediatric medicine. However, this feature is of equal importance in veterinary medicine. For example, in the case of antibiotics such as erythromycin which have an extremely unpleasant bitter taste it is virtually impossible to administer such antibiotics orally to animals because it is not possible to successfully mask the bitter taste. Accordingly, such known oral formulations are rejected by animals.

The present invention therefore in one important aspect provides controlled release antibiotic formulations substantially free from the taste of said antibiotic for pharmaceutical or veterinary use which:

a) are in the form of powders according to the invention;

b) are in the form of non-aqueous suspensions of the powders according to the invention; or

c) are in the form of reconstitutable aqueous suspensions of the powders according to the invention.

The powders according to the invention can be used in pre-mixes for animal feedstuffs and other feed additives.

In addition to drugs, nutritional supplements such as vitamins can be administered orally to animals using the powders according to the invention.

Suitable veterinary preparations according to the invention include veterinary feeds, boluses, drenches and washes.

In the agricultural field the powders according to the invention can also be used for preparation of controlled release herbicides and pesticides.

In the cosmetics field one use of the controlled release powders according to the invention is as sustained release fragrance particles for use in talcum powders, creams, lotions and other cosmetic preparations.

Each of the particles of the controlled release powder according to the invention represents a true micromatrix with the active ingredient and optionally one or more excipients uniformly distributed therethrough as depicted in Fig. 1 of the accompanying drawings which is a half-tone drawing prepared from an electron micrograph of "pharmasomes" containing theophylline and prepared as described in Example 1 below. The theophylline can be observed to form veins or a labyrinth throughout the polymeric material of the "pharmasome". Fig. 2 is a half-tone drawing prepared from an electron micrograph of the "pharmasomes" after the theophylline has been leached out by dissolution in water for 24 hours. One is left with a matrix structure of polymeric material.

The micromatrix nature of the particles can also be demonstrated by their dissolution profile. Referring, for example, to Examples 1 and 2 hereinbelow, it is found that the dissolution rate (D) is directly proportional to the square root of time (t) according to the following equation:

$$D \alpha \sqrt{t}$$

after an initial burst of release of active ingredient which is considered to be active ingredient lying close to the surface of the particles. The dissolution rate is dependent on the amount of active ingredient remaining in the particle matrix at any given time. Theoretically the last molecule of active ingredient never leaches out. The dissolution rate is assumed to reach 100% at infinity.

The particles according to the invention also have a degree of porosity which can be calculated from the absolute density of the particles measured on a pycnometer. The dissolution rate of the particles according to the invention is also found to relate to the degree of porosity of said particles.

The microparticles according to the invention are to be distinguished from microcapsules in that in the latter the active ingredient is encapsulated by a polymer coating, whereas in the former the active ingredient is uniformly distributed throughout the polymeric material as described above and as indicated in Figs. 1 and 2 of the accompanying drawings.

The invention will be further illustrated by the following examples. In the examples the dissolution rate of the various pharmaceutical formulations is measured by the Paddle Method of U.S. Pharmacopoeia XX at 37°C and 75 r.p.m., using 200 mg of sample per 900 ml of simulated intestinal fluid excluding enzymes.

EXAMPLE 1

Preparation of Micro-Particles Containing Theophylline

Theophylline was ground in a motorised ball mill and then sieved through a 38 µm mesh sieve.

Cellulose acetate butyrate (CAB) was dissolved in acetone so as to give a concentration of CAB in acetone of 15% w/v.

Hexane (20 ml) was added to an aliquot of the CAB solution (100 g) with constant stirring.

A portion of the sieved theophylline (10 g) was then added to the polymer solution under constant agitation to ensure an even dispersion of the theophylline. This product constituted an internal phase for the subsequent emulsification step.

Magnesium stearate was dissolved in heavy mineral oil U.S. Pharmaceopoeia so as to achieve a concentration of 1.5% w/v. This solution was used as an external liquid phase. 150 ml of the external liquid phase was decanted into a tall 600 ml beaker and the internal phase prepared above was added thereto. Emulsification was achieved using a Silverson mixer (Silverson is a Trade Mark) at full speed for 2 minutes and then dropping the speed as required to achieve the desired particle size.

The suspension of particles in the external phase was then introduced into a rotary evaporator and the acetone removed under vacuum. The suspension now consisted solely of polymer coated theophylline or "pharmasomes" suspended in the external liquid phase. On microscopic examination particle size was found to range from 10 to 180 m.

The particles were centrifuged down and the external phase decanted. The particles were then washed repeatedly with heptane to remove the external liquid phase. The final product was then filtered and dried at 45°C for two hours. The particles were then sieved with mesh sizes of 50, 90, 125 and 180 µm. The major proportion of particles were retained by the 90 µm sieve.

The dissolution rate of the 90—125 m fraction of the particles was estimated using the Paddle Method of U.S. Pharmacopoeia XX as indicated above. The results were as follows:

Time (h)	% Release
0.5	42
1	57
2	62
3	65
4	69
5	73
6	78
7	85
8	91
9	95
10	97

The particles were found to be tasteless with complete masking of the normally bitter taste of theophylline.

EXAMPLE 2

Preparation of Micro-Particles Containing Paracetamol

Example 1 was repeated except that 20 g of paracetamol was used in place of 10 g of theophylline. In the external liquid phase heavy mineral oil was replaced by light mineral oil. A major proportion of the particles had an average size of 90 µm.

The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0	0
0.5	43
1	55
2	67
3	75
4	80
5	85
6	89
7	91
8	96

The particles were found to be tasteless.

EXAMPLE 3

Preparation of Micro-Particles Containing Nifedipine

Example 1 was repeated except that 16 g of nifedipine was used in place of theophylline. The internal phase consisted of Eudragit RS 100 (Eudragit RS 100 is a Trade Mark) and methanol at a concentration of 33% w/v. The external phase consisted of magnesium stearate in light mineral oil at a concentration of 2.5% w/v.

The dissolution rate of the particles formed was determined and was found to be as follows:

Time (h)	% Release
0.5	25
1	30
2	35
3	55
4	70
6	85

The particles were found to be tasteless.

EXAMPLE 4

Preparation of Micro-Particles Containing Dextromethorphan Hydrobromide

Example 1 was repeated except that 10 g of theophylline was replaced by 10 g of dextromethorphan hydrobromide.

The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0.5	45
1	55
2	70
3	74
4	80
5	—
6	90

EXAMPLE 5

Preparation of Micro-Particles Containing Saccharin Sodium

Example 1 was repeated except that theophylline was replaced by 6.5 g of saccharin sodium. The internal phase consisted of Ethocel (ethyl cellulose) (Ethocel is a Trade Mark) 45 cps dissolved in ethanol so as to give a concentration of 15% w/v. Saccharin sodium was added to 50 g of the polymer solution. The external liquid phase consisted of heavy mineral oil U.S. Pharmacopoeia.

The dissolution rate of the particles was determined and was found to be as follows:

Time (sec.)	% Release
5	60
10	75
15	89
30	94
60	100

EXAMPLE 6

Preparation of Micro-Particles Containing Pseudoephedrine Hydrochloride

The procedure of Example 1 was repeated except that the theophylline was replaced by 10 g of pseudoephedrine hydrochloride. 50 g of CAB was used which was dissolved in 20 ml of hexane so as to form the polymer solution.

The dissolution rate of the particles was determined and found to be as follows:

Time (h)	% Release
0.5	35
1	55
2	60
3	68
4	73
5	80
6	84
7	90
8	94

EXAMPLE 7

Preparation of Micro-Particles Containing Carbinoxamine Maleate

Example 1 was repeated using carbinoxamine maleate in place of theophylline. The dissolution rate of the particles was determined and found to be as follows:

Time (h)	% Release
0.5	20
1	25
2	30
3	45
4	55
5	65
6	70
7	73
8	78

EXAMPLE 8

Preparation of Micro-Particles Containing Guaiphenesin

Example 1 was repeated except that theophylline was replaced by guaiphenesin (12.5 g). The polymer solution consisted of Ethocel (Ethocel is a Trade Mark) (ethyl cellulose) 4 cps dissolved in ether so as to give a concentration of 25% w/v.

The external phase consisted of an aqueous solution of sorbitol 70% w/w (sorbitol solution B.P.)

Upon removal of the solvent of the internal phase the particles or "pharmasomes" remained suspended in the sorbitol solution. The particles were harvested by decanting the sorbitol solution. The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0.5	50
1	55
2	61
3	64
4	70
5	76
6	81
7	87
8	93

EXAMPLE 9

Example 8 was repeated without decanting the sorbitol solution. The suspension thereby obtained was flavoured and made up to the required strength for use as an oral suspension.

EXAMPLE 10

Preparation of Micro-Particles Containing Erythromycin Base

Example 1 was repeated except that theophylline was replaced by erythromycin base. The polymer used was a mixture of cellulose acetate butyrate and cellulose acetate phthalate in a ratio of 2:1. The dissolution rate of the particles was determined and was found to be as follows:

Time (h)	% Release
0.5	20
1	30
2	40
3	55
4	70
5	78
6	87
7	95

Other mixed polymers were used in the internal phase and proved successful in achieving a 100% release of the active ingredient from the particles formed. Examples of mixed polymers used were as follows:

Polymer	Ratio
Cellulose acetate butyrate/polyvinylpyrrolidone	9:1
Cellulose acetate butyrate/polyvinylpyrrolidone	4:1
Cellulose acetate butyrate/Poly(methyl methacrylic acid)	1:1
Cellulose acetate butyrate/Poly(methyl methacrylic acid)	3:1
Eudragit RS/Eudragit RL	9:1
Ethocel/polyvinylpyrrolidone	9:1

EXAMPLE 11

Preparation of Theophylline Syrup

Particles prepared according to Example 1 were suspended in a sugar solution in water (66%) so as to obtain a theophylline syrup containing 200 mg of theophylline per 5 ml of syrup. When administered orally the normally bitter taste of theophylline was completely masked.

Pharmacological Data

The plasma level profile of theophylline was obtained from the mean values obtained for two subjects according to the data listed in Tables 1 and 2. Fig. 3 is a graph of plasma levels (mcg/ml) versus time after administration (hours) for the syrup prepared according to Example 11 based on the values indicated in Tables 1 and 2.

It will be observed from the accompanying Fig. 3 and Tables 1 and 2 that the plasma levels after 10 hours are not significantly different from the plasma levels after one hour. Accordingly, the graph shows a prolonged absorption phase with the minimum of fluctuation of plasma levels over 10 hours. Normally, theophylline (rapid or immediate release) peaks at 2 hours. The apparent biological half-life of theophylline has been found to range from 4—9 hours. One would normally expect half the peak plasma levels by 7 hours and approximately one third of the peak plasma levels by 10 hours.

These results suggest that the syrup prepared according to Example 11 could potentially be dosed quite safely at intervals of 12 hours i.e. twice daily. This is half the dosage frequency of conventional non-sustained or immediate release theophylline.

TABLE 1

Blood Level Study Results—Summary of Pharmacokinetic Data
Theophylline—600 mg S.D.
Plasma Levels mcg/ml
Hours After Administration

SUBJ	0.00	1.00	2.00	4.00	6.00	8.00	10.00
1	0.00	3.15	4.25	4.70	3.45	3.00	2.85
2	0.00	2.90	4.85	5.05	5.00	4.30	4.25
MEAN	0.00	3.03	4.55	4.88	4.23	3.65	3.55
ST DEV	0.00	0.18	0.42	0.25	1.10	0.92	0.99
*CV (%)	0.00	5.84	9.32	5.08	25.94	25.18	27.89
MAX	0.00	3.15	4.85	5.05	5.00	4.30	4.25
MIN	0.00	2.90	4.25	4.70	3.45	3.00	2.85

*Coefficient of variation

TABLE 2
Theophylline—600 mg S.D.
Pharmacokinetic Parameters

	AUC* (0.00—10.00 H)	Peaking Time T(max)	Peak Height C(max)	C(max)/C(min) at 10.00 Hours	Elimination Rate K EL.	Half-Life T 1/2
1	34.67	4.00	4.70	1.65	0.05	14.51
2	43.13	4.00	5.05	1.19	0.03	20.74
MEAN	38.90	4.00	4.88	1.42	0.04	17.62
ST DEV	5.98	0.00	0.25	0.33	0.01	4.41
CV (%)	15.36	0.00	5.08	22.91	25.00	25.00
Based on Mean Blood Level Curve						
MEAN		4.00	4.88	1.37		

*Area under curve

EXAMPLE 12

Theophylline Suspension

Theophylline microparticles "Pharmasomes" (prepared as per Example 1) were suspended in a liquid vehicle consisting of:

70% Sorbitol Solution	89.9% by weight
Glycerin	10.0% by weight
Polysorbate-80 (Trade Mark)	0.1% by weight

so as to give a suspension containing 200 mg theophylline per 5 ml.

Samples of the suspension were stored at room temperature and tested at intervals to determine the stability of the "pharmasomes" in suspension.

At the time of preparation the assayed content of theophylline was 188.4 mg/5 ml and after 15 weeks it was 190.5 mg/5 ml indicating that there had been no chemical breakdown of the drug.

The dissolution rate was also tested over a 15 week period and the results are summarised in Table 3 in Fig. 4.

In summary the data shows that the suspension retains its potency and dissolution characteristics for at least 15 weeks after preparation.

Pharmacological Data

The suspension prepared as per Example 12 was tested in a six subject bioavailability study at a dose of 720 mg (18 ml) versus a conventional syrup (Somophylline) given as two doses of 360 mg at 0 and 6 hours. The results are summarised in Table 4 and Fig. 5. In Fig. 5 the curve (a) represents the suspension of Example 12 and curve (b) the Somophylline syrup used as reference.

TABLE 3
Theophylline Suspension of Example 12 (200 mg/5 ml) Stability of Dissolution
Percentage Dissolution

	Time (Hours) 0.00	1.00	2.00	3.00	4.00	5.00	6.00	24.00
0 Wks	0.00	43.30	59.20	75.60	80.00	84.30	87.70	100.00
3 Wks	0.00	39.50	59.10	70.70	77.90	84.20	87.70	99.50
5 Wks	0.00	40.00	60.10	69.80	78.20	85.10	85.90	99.00
7 Wks	0.00	42.00	63.00	79.20	84.20	90.00	90.60	100.00
15 Wks	0.00	45.80	60.90	72.50	80.70	84.90	88.00	99.90

TABLE 4
Mean Theophylline Plasma Concentration (mcg/ml)

Time (h)	Somophylline	Theophylline Suspension
0.0	0.0	0.0
0.5	7.98	1.38
1.0	10.24	3.57
1.5	8.68	6.09
2.0	8.17	7.31
3.0	7.68	8.81
4.0	5.93	9.75
6.0	5.25	9.17
6.5	10.94	9.75
7.0	11.20	9.08
7.5	11.75	8.84
8.0	12.37	9.14
9.0	11.98	8.37
10.0	10.76	7.52
12.0	8.99	6.26

The data clearly shows that although the theophylline suspension of Example 12 is slightly less bioavailable (87%) than the reference, the time to peak and the duration of significant blood levels is indicative of a twice daily dosage regimen. The usual dosage regimen for theophylline is four times per day.

EXAMPLES 13 and 14

Theophylline microparticles "pharmasomes" were prepared according to Example 1 and screened into two fractions:

Example 13—microparticles having an average particle size of less than 90 microns

Example 14—microparticles having an average particle size of greater than 90 microns.

The "pharmasomes" were suspended in a vehicle made up of:

	% by Weight
70% Sorbitol Solution	85.3
Avicel RC 591 (Trade Mark)	0.7
Potassium Sorbate	0.3
Titanium Dioxide 25% (in 70% Sorbitol)	2.7
Simethicone (Trade Mark) 10% Emulsion	0.01
Glycerin	10.8
Citric Acid	0.3
Sodium Lauryl Sulphate	0.04

so as to produce a suspension containing 300 mg Theophylline per 5 ml.

Pharmacological Data

The suspensions of Examples 13 and 14 were tested for bioavailability in four subjects at a dose of 690 mg (11.5 ml) for the syrups of Examples 13 and 14 versus a conventional syrup (Somophylline) given as two doses of 320 mg at 0 and 6 hours. The results are summarised in Table 5 and Fig. 6. The Fig. 6, the curve (a) represents the suspension of Example 13, the curve (b) the suspension of Example 14 and the curve (c) the Somophylline syrup used as reference.

TABLE 5
Mean Theophylline Plasma Concentration—mcg/ml

Time (h)	Somophylline	Suspension of Example 13	Suspension of Example 14
0	0	0	0
0.5	9.53	2.65	1.98
1	10.14	5.08	4.07
1.5	9.21	6.94	6.45
2	8.64	7.16	6.81
3	7.74	6.93	7.67
4	6.82	7.74	7.99
6	5.21	6.46	7.08
6.5	8.79	—	—
7	12.00	6.74	6.93
7.5	12.01	—	—
8	12.11	6.03	6.47
9	11.61	—	—
10	10.17	5.35	5.82
12	8.07	4.06	5.02
15	—	2.77	4.04
18	—	2.22	2.67
21	2.44	1.79	1.95
24	1.55	1.28	1.59

The results confirm the findings for Example 12 as indicated in Fig. 7, wherein curve (a) represents the suspension of Example 12, curve (b) the suspension of Example 13 and curve (c) the suspension of Example 14.

EXAMPLE 15

Paracetamol Suspension

Paracetamol "pharmasomes" prepared as per Example 2 were suspended in a liquid vehicle prepared as per Example 12 to give a suspension containing 300 mg of Paracetamol per 5 ml.

The suspension was stored at room temperature and tested at intervals for 30 weeks.

At the time of preparation the assayed content was 299.8 mg (paracetamol) per 5 ml and after 30 weeks was 297.9 mg/5 ml indicating that there was no significant loss of activity.

During the above time period the dissolution was also tested and the results are given in Table 6.

TABLE 6
Percentage Dissolution

	Time (h) 0.00	1.00	2.00	3.00	4.00	5.00	6.00
0 Wks	0.00	56.50	70.60	76.00	81.30	83.80	86.30
2 Wks	0.00	58.40	71.80	80.40	81.70	86.40	87.90
5 Wks	0.00	56.90	72.50	77.20	80.40	83.90	84.40
7 Wks	0.00	55.30	69.10	75.40	80.30	82.90	84.70
15 Wks	0.00	58.90	69.30	76.78	80.60	82.80	84.30
30 Wks	0.00	58.10	71.50	76.90	81.90	84.70	87.30

A graphic representation of these results is shown in Fig. 8.

The suspension was tested for bioavailability in 6 subjects at a dose of 1000 mg versus a reference solution (Dozol-Elixir (Dozol is a Trade Mark)) which was given as two divided doses of 500 mg. The results are given in Table 7.

TABLE 7
Mean Paracetamol Plasma Concentrations (mcg/ml)

Time (h)	Reference (Dozol)	Suspension of Example 15
0.0	0.0	0.0
0.5	7.74	3.44
1.0	6.49	6.05
2.0	4.14	7.36
3.0	3.04	5.80
4.0	2.04	4.60
6.0	1.08	3.15
6.5	5.33	2.65
7.0	5.88	2.26
8.0	4.79	1.88
9.0	4.00	1.63
10.0	3.05	1.44
12.0	1.81	1.06
14.0	1.10	0.72
16.0	0.69	0.49
24.0	0.18	0.14

A graphic representation is given in Fig. 9, wherein curve (a) represents the suspension of Example 15 and curve (b) the conventional Elixir.

The data shows that although the suspension of Example 15 is slightly less bioavailable (90%) than the reference, the blood level is maintained for almost twice as long equating to halving of the dosage frequency.

EXAMPLE 16

"Pharmasomes" were prepared as per Example 2 and suspended in liquid as per Example 13 so as to give a suspension containing 320 mg per 5 ml. This suspension was tested for bioavailability in 6 subjects using a conventional (Tylenol (Trade Mark)) Elixir as reference. A single dose of paracetamol "pharmasomes" 2000 mg (31.25 ml) was administered and two doses of Tylenol (1000 mg) at 0 and 6 hours. The results are given in Table 8.

TABLE 8

Mean Paracetamol Plasma Concentrations (mcg/ml)

Time (h)	Reference (Tylenol Elixir)	Suspension of Example 16
0.0	0.0	0.0
0.5	14.33	8.27
1.0	14.05	15.09
2.0	6.69	14.34
3.0	6.95	13.24
4.0	4.93	11.53
4.5	15.53	9.52
5.0	14.67	8.08
6.0	12.72	6.10
7.0	8.92	4.43
8.0	6.61	3.54
10.0	3.64	2.43
12.0	2.17	1.10
14.0	1.31	1.10
16.0	0.77	0.68
24.0	0.02	0.17

The results are presented graphically in Figure 10 wherein curve (a) corresponds to the suspension of Example 16 and curve (b) corresponds to the reference Elixir. The prolonged absorption profile again can be seen with no significant loss in bioavailability, indicating a reduced dosage frequency.

EXAMPLE 17

"Pharmasomes" were prepared as per Example 2 with cellulose acetate being substituted for the cellulose acetate butyrate. The suspension was prepared as per Example 16. The suspension was tested in a 6 subject bioavailability study at a single dose of 2000 mg against a reference solution (Tylenol Elixir) given as two 1000 mg doses. The results are given in Table 9.

TABLE 9
Mean Paracetamol Plasma Concentrations (mcg/ml)

Time (h)	Tylenol Elixir 1 g×2	Suspension of Example 17 2 g×1
0.0	0.00	0.00
0.5	12.30	5.11
0.75	12.88	7.07
1.0	12.29	9.15
1.5	10.17	12.01
2.0	8.19	12.47
3.0	6.00	11.17
4.0	4.35	9.40
4.5	13.54	8.37
4.75	14.00	8.04
5.0	13.02	7.55
5.5	13.09	6.57
6.0	11.20	5.71
7.0	8.17	4.54
8.0	5.98	3.76
10.0	3.42	2.66
12.0	1.98	1.60
14.0	1.24	1.03
16.0	0.82	0.83
24.0	0.26	0.39

The figures given in Table 9 and accompanying Figs. 11 and 12 again demonstrate the prolonged absorption nature of the product. In Fig. 11 curve (a) corresponds to the suspension of Example 19 and curve (b) the reference Tylenol Elixir. In Fig. 12 curve (a) corresponds to the suspension of Example 15, curve (b) to the suspension of Example 16 and curve (c) to the suspension of Example 17.

EXAMPLE 18

Chewing gum containing microparticles of Aspartame were prepared in the following manner.

An internal phase was prepared by dissolving ethylcellulose (45 cps) in sufficient ethanol to produce 200 g of solution. 100 g of Aspartame (Particle size less than 60 microns) was dispersed in 300 g of acetone. The two liquids were then mixed by mechanical agitation. The external phase was prepared according to Example 1, 2 litres being required. The internal and external phase were mixed by mechanical agitation and then passed through an emulsifier. The emulsion was placed in a vacuum and the solvents (acetone and ethanol) evaporated. The Aspartame/ethylcellulose microparticles were harvested by centrifugation.

To evaluate the Aspartame-containing "pharmasomes", unsweetened chewing gum was used. Pure Aspartame powder and the prepared "pharmasomes" were folded into the gum so as to give a 0.2% concentration of Aspartame. Both types of gum were chewed by a panel of 24 volunteers in a blind, crossover manner. The volunteers were asked to report their perception of the intensity (on a scale of 0 to 10) and duration of sweetness. On average the duration of sweetness for the pure Aspartame-containing

gum was 10 minutes. The gum containing the "pharmasomes" was perceived as being less intensely sweet but observably sweet for 30 minutes on average. The results are indicated in Fig. 13 which is a graphic representation of the Aspartame sweetness test giving mean values for the testing panel of 24 volunteers.

EXAMPLE 19

Chewable Tablet Containing Paracetamol

The following materials were mixed together:

1000 g Paracetamol "pharmasomes"—as per Example 2 (equivalent to 500 g of Paracetamol)
250 g Dipac (Trade Mark) (Sucrose 97%, Dextrin 3%)
250 g Mannitol
5 g Colloidal Silicon Dioxide
25 g Maize Starch
20 g Magnesium Stearate
15 g Orange Flavour
35 g Orange Colour

The blend was compressed at a weight of 960 mg into tablets each containing 300 mg of Paracetamol. The tablets were pleasant to chew and the dissolution characteristics of the "pharmasomes" were unchanged as shown in Table 10 and Fig. 14.

TABLE 10
Dissolution Rate

Time (h)	"Pharmasomes"	Tablets
1	58.7%	59.2%
3	79.8%	80.7%
6	95.6%	95.8%

In Fig. 14 curve (a) corresponds to the dissolution pattern of the "pharmasomes" of Example 19 and curve (b) to the chewable tablets prepared therefrom.

EXAMPLE 20

"Melt" Tablets Containing Paracetamol

Melt tablets are similar to chewable tablets except that they disintegrate rapidly in the mouth and do not need to be chewed. Such tablets were prepared as follows:

1000 g Paracetamol "pharmasomes" (as per Example 2) (equivalent to 500 g Paracetamol)
50 g Mannitol
250 g Microcrystalline Cellulose
30 g Strawberry Flavour
15 g Red Colour
60 g Cross-Povidone
5 g Sodium Lauryl Sulphate
30 g Carboxymethyl starch
15 g Magnesium Stearate
15 g Talc

The blend was compressed at a weight of 882 mg to give tablets each containing 300 mg of Paracetamol. The disintegration time of the tablets was less than 30 seconds and the dissolution rate of the "pharmasomes" was unchanged as indicated in Table 11 and Fig. 15.

TABLE 11
Dissolution Rate

Time (h)	"Pharmasomes"	Tablets
1	58.7%	60.1%
3	79.8%	81.2%
6	95.6%	95.5%

In Fig. 15 curve (a) corresponds to the dissolution pattern for the "pharmasomes" of Example 20 and curve (b) to the melt tablets prepared therefrom.

EXAMPLE 21

Capsules Containing Nifedipine

"Pharmasomes" were prepared as per Example 3. By nature they were free flowing and only 0.5% magnesium stearate needed to be added to prevent sticking during capsule filling. The equivalent of 20 mg of Nifedipine was encapsulated into size No. 4, two piece hard gelatin capsules. The dissolution rate remained unchanged as shown in Table 12 and Fig. 16. In Figure 16 curve (a) corresponds to the dissolution pattern for the "pharmasomes" of Example 21 and curve (b) to the capsules prepared therefrom.

TABLE 12
Dissolution Rate

Time (h)	"Pharmasomes"	Capsules
0.5	42.6%	41.7%
1	56.1%	54.9%
3	74.6%	73.6%
5	85.9%	84.4%
8	98.7%	97.6%

Although not wishing to be bound by any theoretical explanation of the invention, it is believed that the polymer substantially but not entirely coats the active ingredient, because a 100% release of active ingredient can be achieved even when an insoluble polymer is used.

EXAMPLE 22

Non-Aqueous Suspension of Potassium Chloride

A non-aqueous suspension of potassium chloride—containing "pharmasomes" was prepared, having a concentration of potassium chloride of 300 mg/5 ml and which in addition to the "pharmasomes" contained the following ingredients:

Oil USP (Soy, cotton seed)	425.00 ml
Sorbitol Powder USP	100.00 g
Aerosil R972 (Trade Mark)	12.50 g
Tenox GT1 (Trade Mark)	0.20 g
Citric acid	0.025 g
Chocolate flavour # 396676	0.52 ml
Chocolate mint flavour # 395496	0.37 ml
Flavour enhancer	1.00 g
Brown Lake dye	0.05 g
Titanium dioxide	0.10 g

The total volume of the suspension without the "pharmasomes" was 500 ml.

The Sorbitol powder USP and Aerosil R972 (Trade Mark) were dry blended and then ball milled with the oil mix to produce an even dispersion. The Tenox GT1 (Trade Mark) which is an anti-oxidant and the citric acid were dry blended and then dispersed with constant agitation into the oil mixture. The chocolate and chocolate mint flavours and the flavour enhancer were then dispersed into the oil mixture. Finally, the Brown Lake dye and the titanium dioxide were added to the oil mixture and the resultant mixture was agitated for one hour to ensure even dispersion of the various ingredients. An amount of potassium chloride—containing "pharmasomes", prepared according to the procedure described in Example 1 but substituting potassium chloride for theophylline, and equivalent to 300 mg potassium chloride per 5 ml was blended together with the oil mixture resulting in an evenly mixed suspension.

CLAIMS

1. A controlled release powder containing discrete micro-particles for use in edible, pharmaceutical and other controlled release compositions, said powder comprising particles containing an active ingredient and optionally an excipient in intimate admixture with at least one non-toxic polymer, each of said particles being in the form of a micromatrix with the active ingredient and the excipient, if present, uniformly distributed throughout the polymer, said particles having an average size in the range 0.1 to 125 µm, and having a predetermined release of active ingredient when the dissolution rate thereof is measured according to the Paddle Method of U.S. Pharmacopoeia XX at 37°C and 75 r.p.m.

2. A controlled release powder according to claim 1, wherein the particles have an average size in the range 5 to 100 µm.

3. A controlled release powder according to claim 1 or 2, wherein the active ingredient is a drug, a nutrient, a flavouring agent or a sweetening agent.

4. A controlled release powder according to Claim 1 or 2, wherein the active ingredient is a colouring agent, a fragrance, a herbicide or a pesticide.

5. A controlled release powder according to any one of claims 1 to 4, wherein the polymer is selected from: alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic acids and esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes and polyurethanes and co-polymers thereof.

6. A process for preparing a controlled release powder according to any one of claims 1 to 5, which comprises the steps of:

a) forming a solution of the polymer or polymers in a solvent;

b) dissolving or dispersing the active ingredient in said polymer solution so as to form a uniform mixture; and

c) removing the solvent from the mixture so as to obtain micro-particles having an average size in the range 0.1 to 125 µm.

7. A process according to claim 6, wherein the particles obtained have an average size in the range 5 to 100 µm.

8. A process according to claim 6 or 7 wherein the solvent is selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof, and the solvent is removed in step (c) by spray drying, use of an external liquid phase, phase separation, interfacial polymer deposition or coacervation.

9. A pharmaceutical composition containing a controlled release powder according to any one of claims 1 to 5.

10. A pharmaceutical composition containing a controlled release powder according to any one of Claims 1 to 5, and which is in the form of tablets, capsules, suppositories, implants or ocular inserts.

11. A pharmaceutical composition according to Claim 9, which is in the form of chewable tablets or melt tablets.

12. A pharmaceutical composition containing a controlled release powder according to any one of claims 1 to 5, and which is in the form of a cream, an ointment or a formulation suitable for transdermal delivery.

13. A pharmaceutical composition containing a controlled release powder according to any one of claims 1 to 5, and which is in the form of a liquid for oral, local or parenteral administration.

14. A pharmaceutical composition according to claim 13, which is in the form of eye drops, nasal drops, ear drops, a suspension, a syrup, or an infusion or injectable solution.

15. A pharmaceutical composition according to any one of claims 9 to 14, wherein the active ingredient is selected from: ibuprofen, paracetamol, 5-amino-salicylic acid, dextromethorphan, propranolol, theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diazepam, diclofenac, indomethacin, amoxycillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, lincomycin, codergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, erythromycin stearate, lorazepam, glibenclamide, salbutamol, trimethoprim/sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin and metoprolol tartrate.

16. A pharmaceutical composition according to Claim 9 for oral administration, wherein the active ingredient is theophylline.

17. A pharmaceutical composition according to Claim 9 for oral administration, wherein the active ingredient is paracetamol.

18. A pharmaceutical composition according to Claim 9 for oral administration, wherein the active ingredient is potassium chloride.

19. A controlled release powder according to claim 1, substantially as hereinbefore described with reference to the Examples.

20. A process according to Claim 6 for preparing a controlled release powder, substantially as hereinbefore described with reference to the Examples.

21. A controlled release powder whenever prepared by a process claimed in any one of Claims 6 to 8 and 20.

22. A pharmaceutical composition according to Claim 9, substantially as hereinbefore described with reference to the Examples.

23. An oral formulation for administration to human and non-human animals which is substantially free of the taste of the active ingredient comprising a controlled release powder according to any one of Claims 1 to 5 and 19.

24. An oral formulation according to Claim 23 which is in the form of a liquid, chewable tablet, melt tablet, foam, gel or gum.

25. A chewable gum which contains as sweetening agent aspartame-containing microparticles according to any one of Claims 1, 2, 3 or 5.

26. A non-aqueous suspension of a highly water-soluble or water-insoluble active ingredient, wherein the active ingredient is in the form of microparticles of a controlled release powder according to any one of Claims 1 to 5.

27. A non-aqueous suspension according to Claim 26, wherein the highly water-soluble active ingredient is selected from: dextromethorphan, guaiphenesin and pseudoephedrine and salts thereof and potassium chloride.

28. A controlled release antibiotic formulation substantially free from the taste of said antibiotic for pharmaceutical or veterinary use which comprises a controlled release powder according to any one of Claims 1, 2, 3 or 5.

29. An antibiotic formulation according to Claim 28, wherein the powder is in the form of a non-aqueous suspension.

30. An antibiotic formulation according to Claim 28, which is in the form of a reconstitutable aqueous suspension.

31. An oral formulation according to Claim 23, substantially as hereinbefore described with reference to the Examples.

32. A chewing gum according to Claim 25, substantially as hereinbefore described with reference to Example 18.

33. A non-aqueous suspension according to Claim 26, substantially as hereinbefore described with reference to Example 22.

34. A controlled release antibiotic formulation according to Claim 28, substantially as hereinbefore described.

35. A controlled release formulation according to any one of claims 1 to 5 and 9 to 34 or produced according to any one of Claims 6 to 8 for use in the treatment of the human or animal body by therapy.

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